

# The effect of laparoscopic ovarian drilling on timing of menopause in patients with polycystic ovary syndrome: 29 years of follow-up data

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**Background:** Despite significantly improved rates of ovulation and pregnancy after laparoscopic ovarian drilling (LOD) in patients with polycystic ovary syndrome (PCOS), one should remain cautious of this procedure due to the associated risk of post-operative adhesions and a significant decrease in ovarian reserve markers. In this longitudinal follow-up study, we aimed to evaluate the long-term effects of LOD on the timing of menopause. **Methods:** A total of 83 patients were identified who had undergone LOD between December 1991 and December 1996. Of the 13 patients that we were able to reach, two had undergone unilateral LOD and were excluded, leaving 11 patients to be analysed. **Results:** The median age at the time of LOD was 25 (range 19–35) years. The median age at the time of the current analysis was 52 (range 46–64) years. Whereas two of these patients had surgical menopause at the age of 35 and 47 due to leiomyoma, four patients had natural menopause between the ages of 45 to 52 years. Although five patients were still having regular cycles at the age of 46 to 54 years at the time of the study, we do not have any biochemical data to evaluate their ovulatory status. With respect to fecundity, whereas nine out of 11 patients conceived spontaneously, two required assisted reproduction treatment. **Discussion:** According to the findings from a limited number of patients, LOD does not appear to have any negative effect on the timing of menopause.

## Keywords

Laparoscopic ovarian drilling; Polycystic ovary syndrome; Menopause

## 1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women [1]. In 1935, when PCOS was originally defined by Stein and Leventhal [2], seven women with enlarged ovaries, menstrual disturbances  $\pm$  hirsutism, were treated with bilateral ovarian wedge resection. After treatment, all had regular cycles and five of them conceived during the follow-up period. In 1984, 62 women with PCOS were treated by laparoscopic systematic electrocautery of the ovarian capsule. Following treatment, ovulation occurred in 92% of the patients and pregnancy was achieved in 69% of the women who wished to conceive [3].

Despite a significant improvement in ovulation and preg-

nancy rates after LOD, the associated complications, risk of post-operative adhesions, significant decrease in ovarian reserve markers, and later the introduction of clomiphene citrate, have limited its use in recent years [4]. Currently, although clomiphene citrate (CC) or letrozole is recommended as first-line treatment for women with PCOS, laparoscopic ovarian drilling (LOD) as an alternative approach to exogenous gonadotropin, might still be preferred in the context of second-line treatment, particularly for women who fail to ovulate after taking antioestrogen pills [3–5]. The advantages of LOD include a lower risk of higher-order multiple gestations, avoidance of ovarian hyperstimulation syndrome (OHSS), no requirement to monitor follicular growth, and the persistence of ovulatory cycles for many years without any medication [5]. In addition, LOD might reduce the cost of reaching an ongoing pregnancy with a time horizon of 12 months [6].

Although several follow-up studies have provided evidence for short-term reproductive and endocrinological benefits of LOD [7–9], there are some data that indicate a decline in ovarian reserve markers [10, 11] and one report describes severe ovarian atrophy after the use of a high level of energy [12]. Therefore, the amount of energy applied during the procedure might be critical to produce a treatment effect without impairing the ovarian reserve. Nevertheless, in the recent international evidence-based guidelines for the assessment and management of PCOS, the editors highlighted the small risk of reduced ovarian reserve or loss of ovarian function [13]. In the current study, we aimed to evaluate the fertility performance and menopause status of women with PCOS who had been treated with LOD with a median (minimum to maximum) time period of 27 (25–27) years ago.

## 2. Material and methods

### 2.1 Participants

All patients who had undergone LOD in the Department of Obstetrics and Gynecology, School of Medicine, Hacettepe University, were retrospectively scrutinized using the hospital database and patient files. Although a total of 83 pa-

tients with PCOS who underwent LOD between January 1991 and December 1996 were identified, we failed to retrieve a home/business address or contact number for 62 of the patients. Of the remaining 21 patients, eight did not have an updated contact number and therefore we were only able to reach 13 patients. Of these, two had only undergone unilateral LOD and were excluded. The remaining 11 patients were analysed.

The women were contacted by telephone. If they agreed to participate in the study, they were asked to complete a questionnaire to assess current age, total number of gravidity/parity, age at the time of LOD, smoking history, current menopause status, and necessity for assisted reproduction during reproductive years.

### 2.2 Operational procedure

In some patients, laparoscopic ovarian electrocautery had been performed using a three-puncture technique. The electrosurgical unit employed was Martin-Elmed ModelSystem 2000, Elektrotom 170 (Martin Medical Electronics, Tuttlingen, Germany). The current used had the following features: nominal frequency  $500 \pm 50$  kHz, impulse frequency modulation  $30 \pm 5$  kHz, crest factor 7, duty cycle 1, and high frequency output 80 W max/500. A current generating 70 W was applied for 2 to 4 seconds through the laparoscopic unipolar cautery (Karl Storz GmbH, Tuttlingen, Germany) creating 20 to 25 cautery points (diameter approximately 3 mm, depth 2 to 4 mm) on each ovary. Other patients had been treated using a noncontact technique to apply Nd:YAG laser energy (MBB-Medizintechnik GmbH, Medical Technology, Medilas 2, Munich, Germany). A sterile quartz glass fibre 0.6 mm in core diameter was passed through the operating channel of the laparoscope using a special laser fibre steering device with a deflectable tip (Karl Storz GmbH). The power ranged between 30 and 60 W. The focused laser beam was used from a distance of 5 to 10 mm to create 20 to 25 holes on the surface of each ovary. The laser effect was observed by the blanching of the ovarian surface. Both ovaries were irrigated with heparinized Ringer's lactate solution (5000 U in 1000 mL). Those surgical procedures were performed by various surgeons but with a uniform manner as defined above.

### 2.3 Definition of outcome measures

Gravidity was defined as any conception according to urine/serum pregnancy test. Parity was defined as a gestation exceeding the 20th week of age and/or birth of an infant of more than 500 g. Menopause was defined as the condition of amenorrhea lasting for at least one year. Spontaneous menopause before the age of 40 years was defined as premature ovarian failure (POF).

All patients gave written informed consent to participate in the study and protocol was approved by the Non-Interventional Clinical Research Ethics Board with the registration file number of 2019/07-33 (GO-19/253).

## 3. Results

The median female age at the time of current analysis was 52 (range 46–64) years. The median age at the time of LOD was 25 (range 1935) years. When excluded cases were also analysed for their demographic features in order to confirm the representativity of our included cases, the median ages of the whole group were 26 (range 20–37) and 55 (range 45–66), respectively. These values are similar to our included cases.

The median body mass index was 29.1 (range 25.4–36.8)  $\text{kg/m}^2$  at the time of the current analysis. Of the 11 women, patients 1 and 9 had surgical menopause at the age of 35 and 47, respectively. Notably, patient number 1 had abdominal hysterectomy due to leiomyoma and prophylactic salpingo-oophorectomy. Patient number 9 had abdominal hysterectomy and bilateral salpingo-oophorectomy due to bilateral endometrioma and chronic pelvic pain (Table 1). Of the remaining nine women, four experienced natural menopause when they were between 45 to 52 years (Table 1). Although five patients were still having regular cycles at the age of 46 to 54 years at the time of the study, we do not have any biochemical data to evaluate their ovulatory status. The median menopausal age of their mothers was 48 (range 45–55) years.

Of the patients wishing to conceive, two had undergone assisted reproduction treatment due to failure to conceive after the LOD. Of these, one woman had conceived and one woman had failed to conceive. Nine patients had conceived naturally (Table 1). The corresponding number of gravidity and parity for each patient are also given in Table 1.

## 4. Discussion

As already reported, patients with PCOS may reach menopausal status later than otherwise healthy women [14]. According to one study which included 27 women that had been diagnosed with PCOS 24 years earlier, whereas the mean menopausal age was  $53.3 \pm 2.2$ , it was  $49.3 \pm 2.3$  years in the control group ( $p < 0.01$ ) [15]. In the current study, we saw a similar menopause age after a long-term follow-up among patients treated with LOD, compared with patients who had not undergone any ovarian surgery [15]. According to the available data, a decline in fertility begins around the age of 37–38, and menopause follows approximately 13 years later at, on average, the age of 51 years [16]. Nevertheless, in our study cohort with a median age of 52, four patients had natural menopause between the ages of 45 to 52 years, and five patients were still having regular cycles at 45 to 53 years. The favourable fecundity performance that was achieved spontaneously in this cohort was another significant finding that might encourage the use of LOD in well-selected cases.

As already established, PCOS is the most frequent endocrinopathy among reproductive-aged women [1]. In 2010, a total of 116 million women worldwide were diagnosed with PCOS, according to the World Health Organization [17]. For anovulatory women with PCOS, antioestrogen pills have been recommended as first-line treatment for infertility in

**Table 1. Review of eleven cases with documented menopause status and obstetric outcome after LOD.**

Patient no.	Age at LOD	Menopause age	Current age	No. of total pregnancy	No. of pregnancy after LOD	ART after LOD	Smoking status
1	24	47 (S)	52	2	2	0	(+)
2	35	45	64	0	0	1	
3	25	51	54	1	1	0	(+)
4	19	-	46	3	3	0	(+)
5	26	-	54	2	2	0	
6	25	51	52	1	1	0	
7	20	-	46	3	3	0	(+)
8	29	52	56	2	1	0	(+)
9	33	35 (S)	59	3	2	0	
10	22	-	47	4	4	0	
11	21	-	46	2	2	1 (LB)	

S, surgical menopause; LOD, Laparoscopic ovarian drilling; LB, Live birth.

addition to lifestyle management [18]. In recent years, this first-line treatment has tended to be letrozole due to the associated live birth rate as compared with clomiphene citrate (OR 1.68, 95% CI: 1.42 to 1.99) [19]. However, in patients who fail to ovulate or fail to conceive with antioestrogen pills, either LOD or exogenous gonadotropin treatment might be employed as second-line treatment [18]. When compared with exogenous gonadotropin treatment, the main advantages of LOD include lower multiple pregnancy rates [20], reduced risk of cycle cancellation due to hyperstimulation, and no requirement to monitor follicular growth [21]. Furthermore, according to an economic analysis of a randomized sample of 168 women, LOD might significantly yield a lower cost per first live birth when compared with exogenous FSH treatment (mean difference €3247; 95% CI: €650–€5814,  $p < 0.05$ ) [9].

Despite the well-documented advantages of LOD, a possible decrease in ovarian reserve markers is a disadvantage of the intervention that might obscure the future fertility potential. A recent meta-analysis of seven studies consistently showed a statistically significant fall in serum AMH concentration after LOD (WMD -2.13 ng/mL; 95% confidence interval (CI) -2.97 to -1.30) [10]. This was irrespective of duration of follow-up, type of AMH assay, laterality of surgery, and amount of energy applied during LOD. There are also reports under systematic review that depict a statistically significant difference between Day 3 FSH, inhibin B levels, ovarian volume and antral follicle count before and after LOD [11]. However, whilst LOD seems to significantly influence ovarian reserve markers, it remains uncertain whether this reflects real damage to ovarian reserves or normalization of high pre-operative serum AMH levels that might inherently inhibit initial follicle recruitment, FSH-dependent growth and selection of preantral follicles. In this context, the amount of energy applied during the procedure might be critical in order to observe the effect of treatment without impairing the ovarian reserve. The amount of thermal energy (J) used in LOD can be calculated by multiplying power (W) by duration (s) for each puncture [11]. When this formula is applied to the available data, it can be seen that the energy

level used varies between surgeons. However, severe ovarian atrophy has been reported after 16,000 J (8 holes x 400 W x 5 s) [12].

Other than a post-interventional drop in ovarian reserve markers, postoperative adhesion formation has also been suggested as a condition that might negatively affect the likelihood of conception. In an earlier study of 40 anovulatory women with CC resistance, patients were randomly assigned to have either (i) second-look laparoscopy with lysis of adhesions within three to four weeks of the initial laparoscopy or (ii) expectant management [22]. In the second-look laparoscopy arm, 14 patients had minimal to moderate adhesion formation and three patients had none. Notably, there were no cases with severe adhesion. Of interest, when laparoscopic adhesiolysis was performed with second-look laparoscopy, the subsequent conception rates within six months were comparable with the expectant management arm (47% vs 55%,  $p > 0.05$ ) [22]. These limited data suggest that although there might be some degree of adhesion formation after LOD, it does not appear to be severe and does not have a detrimental effect on the overall conception rate.

The obvious limitation of the current study is the small sample size. Since we aimed to evaluate the time of menopause in patients who had undergone LOD, we enrolled patients who were the first to receive surgery at our institute. Therefore, we were only able to reach a limited number of patients via patient files and contact numbers. Although the median (minimum–maximum) age of the whole group ( $n = 83$ ) at the time of surgical procedure were similar among patients who were analysed ( $n = 11$ ), the representativity of the study group should be questioned and expressed as another limitation in addition to the retrospective design, possibility of recall bias and self-reported data on menopausal status without blood work-up. However, since there have been no published prospective long-term LOD follow-up studies, we believe that our retrospective data is valuable with respect to menopausal age and conception rate. With regard to the absence of a control group, since LOD is usually performed on clomiphene-failed patients, we could not identify a control group of women in which exogenous gonadotropin was pre-

ferred as an alternative strategy in the second step. Since the computer-based file system and ICD coding were not available 29 years ago, it was not possible to properly screen and identify those patients. Whilst we could have used a control group comprising otherwise healthy women who had been admitted to the outpatient clinic during the same period, the measurement of androgens and examination with ultrasonography was missing in those patients and therefore it was not possible to exclude the risk of PCOS.

In conclusion, our results suggest that patients undergoing LOD appear to have favourable conception rates and the procedure itself does not have any negative effects on menopausal age when compared with the data obtained from large-scale cohort studies.

## Abbreviations

LOD, Laparoscopic ovarian drilling; PCOS, polycystic ovarian syndrome; AMH, anti-Müllerian hormone; CC, clomiphene citrate; POF, premature ovarian failing.

## Author contributions

GÖ, GB and SM designed the research study. FA and PC provided help in the data collection. GB, GÖ and HY wrote the manuscript and acted in editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

All patients gave written informed consent to participate in the study and protocol was approved by Hacettepe University Non-Interventional Clinical Research Ethics Board with the registration file number of 2019/07 (GO-19/253).

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## Conflict of interest

The authors declare no conflict of interest.

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